THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

DECEMBER, 1917

ORIGINAL ARTICLES

THE BROADER ASPECTS OF HEMATOLOGICAL DIAGNOSIS.

By E. E. Butterfield, M.D.,

AND

Ralph G. Stillman, M.D.,

NEW YORK.

(From the Medical Divisions and the Pathological Laboratory of the New York Hospital.)

The morphological blood picture generally reflects certain changes in the blood-forming organs, and all that a morphological study really permits in the line of diagnosis is a probable forecast as to the nature of these changes. It is a fortunate coincidence in some cases that the blood picture is sufficiently characteristic to enable one to make a clinical diagnosis on the morphological appearance alone. The extension of our knowledge along these lines has brought to light many cases in which the application of the usual criteria of blood examination has led to an erroneous diagnosis. The tendency has been to rely too much upon the morphological examination of the blood by an expert and to lose sight of the fact that qualitative and quantitative changes in the morphology of the blood are merely an index of more fundamental changes in the blood-forming organs, and that these in turn are due to the presence of some underlying disease of either definite or obscure etiology. With these reservations, and with similar reservations applied to the bacteriological, serological, physical, and chemical examination of the blood, there is probably no organ or system of organs or

structures which affords as many valuable diagnostic criteria as does the blood. The importance and utility of bacteriological and serological examinations need no further comment at this time. The development of accurate methods, especially as applied to small quantities of blood and the convenience of their application, has greatly increased the importance of the physical and chemical study of this fluid, and with the information thus obtained it has been found that the value of such examinations may be greater in some cases than the corresponding study of the excretions. Symptomatic conditions like hyperglycemia, acidosis, uremia, hydremia, etc., may be diagnosed with considerable rapidity and precision exclusively by an examination of the blood.[1] [2] Inasmuch as each one of these conditions is usually associated with a corresponding clinical entity, a correct clinical diagnosis may often be made or confirmed by a properly conceived analysis of the blood alone.

A single morphological criterion rarely permits of as simple and clean-cut interpretation as a properly selected physical or chemical quantity. In morphological hematology it is necessary to work with the number and direction of groups of transitions in form and staining properties, and to correlate these changes with the qualitative and quantitative structural changes in the blood-forming organs. Therefore a clear understanding of the pathological morphology of the blood logically presupposes a knowledge of the histopathology of the blood-forming organs. The interpretation of the somewhat complex histopathology of the blood-forming organs may be greatly facilitated by a study of the fundamental phenomena of hematogenesis. It cannot be urged too strongly that prospective hematologists familiarize themselves first with the appearance of fetal blood and the blood formation in the liver and spleen of the human fetus before the bone marrow has appeared. The development and distribution of the lymph nodes in the human fetus at different ages is also worthy of careful study. In the following brief *résumé* of the histopathology of the blood-forming organs, certain arbitrary distinctions and restrictions are made solely in the interest of simplicity and uniformity in nomenclature without intentional prejudice to one or another of the so-called hematological schools or doctrines. In the examination of a large hematological material one will find that these distinctions and restrictions are not only justifiable but also decidedly useful.

Blood-forming tissue occurs in two essential types, lymphatic and myeloid. *Lymphatic tissue proper* is homogeneous and uniform in structure, and consists chiefly of small lymphoid cells identical

[1] Van Slyke, D.D., Stillman, E., and Cullen, G. E.: The Nature and Detection of Diabetic Acidosis, Proc. Soc. Exper. Biol. and Med., 1915, xii, 165.

[2] Butterfield, E. E., Erdwurm, F., and Braddock, W. H.: The Differentiation of Nephropathies, Cardiopathies, and Allied Conditions, Am. Jour. Med. Sc., 1916, cli, 63.

with the lymphocytes of the peripheral blood. The Malpighian corpuscles of the spleen and the follicles of the lymph nodes and of the intestinal lymphatic structures are prototypes of this tissue. In addition there are small, apparently isolated, groups of lymphoid cells scattered throughout the organs and tissues of the body. The *interfollicular tissue* is not classed with the lymphatic tissue proper on account of the absence or scarcity of small lymphocytes, the lack of homogeneity in structure, and its essentially different behavior under pathological conditions. The term lymphocyte is restricted to cells identical with the small lymphocyte of normal adult human blood. These restrictions are justified by the following facts: (1) in the majority of cases of lymphatic leukemia and lymphatic pseudoleukemia the newly formed tissue is remarkably simple and uniform in structure, and consists chiefly of cells which are identical in morphology with the lymphocytes of normal blood; germinal centers and large lymphocytes are absent; (2) in the development of the lymphatic structures in the human embryo neither germinal centers nor large lymphocytes are demonstrable; (3) there is no evidence of the regular participation of the germinal centers in the proliferation of lymphatic structures, nor is there sufficient evidence that the hypothetical large lymphocyte, supposedly identical with the cells of the germinal centers and the parent cell of both lymphocytes and myelocytes, is necessary for lymphocytogenesis. The identity of the cells of the germinal centers with the elusive large lymphocyte or with the lymphoblast is by no means proved, and the morphological characteristics claimed for the lymphoblast are neither sufficient to differentiate the lymphoblast from other cells, notably the undifferentiated cells of the myeloid group, nor to express the genetic relationship of the lymphoblast to the small lymphocyte.

Pale areas occurring in the lymph follicles in status lymphaticus and in local inflammatory conditions are often called germinal centers by the pathologist. These pale areas are loose in structure and often present signs of necrosis, while signs of active lymphocytogenesis are lacking. They are quite different from the germinal centers described by Flemming, and it is a question whether they are not regressive pathological structures due to local toxic effects or circulatory disturbances in the lymph node.

In contradistinction to the simplicity and uniformity of lymphatic tissue proper, *myeloid tissue* is characterized by its morphological heterogeneity and variegation. This is due to the coexistence of two essentially different groups of cells, namely, those of the erythroblastic group and those of the leukoblastic group. Each of these groups is made up of an *infinite series of morphological transitions*, commencing in an undifferentiated cell with basophilic protoplasm and terminating in a highly differentiated end-product with specific microchemical properties. It is folly to attempt to

attach a special name to each cell representing a stage in this series of transitions. It is more important to be able to recognize the *trend of the transitions* and to be able to tell roughly how far the majority of the cells have progressed in their development. The transition pictures occur both in the erythroblastic and in the leukoblastic groups, but there is no crossing from group to group. The close proximity of the elements of each group to one another in the myeloid tissue probably accounts for the fact that marked proliferation of one group is always accompanied by signs of proliferation in the other group. The earliest recognizable stage of erythrogenesis is represented by a mononuclear basophilic cell devoid of hemoglobin. Nevertheless, the characters of the nucleus as well as those of the protoplasm are sufficient to differentiate these cells from the earliest recognizable cells of the leukoblastic series. Whether or not the earliest differentiable members of these two groups are preceded by a common parent cell is not known. Up to the present time, at least, there is no conclusive evidence in favor of a common direct parent of the erythroblastic and leukoblastic groups. In fact, what evidence there is favors an early independence and autonomous growth of the two groups.[3]

The appearance of newly formed myeloid tissue varies according to whether the hyperplasia is predominantly erythroblastic or leukoblastic. The erythroblastic type of myeloidosis is found in pernicious anemia, von Jaksch's anemia of children[4] in severe septic anemias, and in the regeneration following repeated losses of blood.[5] The leukoblastic type of myeloidosis is found particularly in myeloid leukemia and to a less degree in many infectious diseases.

Hyperplasia of the bone marrow is, of course, the most frequent example of local myeloidosis. When the hyperplasia of the bone marrow is inadequate, or, for reasons unknown, does not occur, or is prevented mechanically, myeloid tissue makes its appearance in the spleen and liver, sites in which it was present in intra-uterine life. Osteosclerosis is an example of mechanical obliteration of bone marrow followed by myeloidosis of the spleen and liver. In the spleen the myeloid tissue is found in the pulp and not in the follicles; in fact, progressive myeloidosis of the pulp encroaches on the follicular borders even to the point of practically complete obliteration of the follicular elements. In the liver, myeloid tissue is found either as intracapillary islands or as loose masses in the periportal spaces. Myeloid tissue is found less frequently in more aberrant sites: the *interfollicular* tissue of the lymph nodes, the *perifollicular* tissue of the lymphoid structures in the intestine, in

[3] Stockard, C. R.: Am. Jour. Anat., 1915, xviii, 227 and 525.

[4] Stillman, R. G.: A Study of von Jaksch's Anemia, Am. Jour. Med. Sc., 1917, cliii, 218.

[5] Skornjakoff: Deutsch. Arch. f. klin. Med., 1911, ci, 251. Milne: Jour. Exper. Med., 1912, xvi, 325.

the obliterated appendix, and in sites of pathological ossification, *e. g.*, laryngeal cartilages.

Typical pernicious anemia, with a high color-index and leukopenia, or typical myeloid leukemia, with a predominance of definite myelocytes, present no difficulties in diagnosis. It is the leukemias with a predominance of undifferentiated cells and the anemias with subleukemic blood pictures which necessitate extreme care in diagnosis and classification. A few cases will serve to illustrate these points.

CASE I.—*Acute myeloid leukemia with a predominance of undifferentiated non-granular cells.* I. A., female, aged five years, a patient of Dr. Frank Erdwurm, was taken sick on July 4, 1914, with pain in the right ankle, difficulty in walking, fever, bleeding from the mouth and nose, and progressive weakness.

Status on August 30. The patient is an emaciated child with a protuberant abdomen. The skin shows numerous hemorrhages varying in size from that of the point of a pin up to 1 cm. in diameter, and there are hemorrhages in the mucous membrane of the mouth. The teeth are normal. The heart is enlarged and there are signs of fluid in both chests and in the abdomen. The lower edge of the liver reaches to the umbilicus while the spleen extends to below that level. The superficial lymph nodes are all slightly enlarged.

The urine contained albumin and casts. The temperature varied between 100° and 104°. She was treated by cataphoresis, according to the method of Veraguth, and died on September 18, 1914. The blood examination showed 1,650,000 red cells with a hemoglobin of 31 per cent. and 99,000 white cells. The differential count was as follows:

Mononuclear non-granular cells	92.0	per cent.
Neutrophilic myelocytes	2.7	"
Polynuclear neutrophiles	3.2	"
Lymphocytes	1.7	"
Mononuclear eosinophiles	0.2	"
Polynuclear eosinophiles	0.2	"

Two nucleated red cells of the megaloblastic type were seen while counting 1087 white cells.

The predominating cell is of extremely variable morphology. The average size is larger than that of a polymorphonuclear leukocyte, although smaller forms are numerous and extremely large forms are not infrequent. The nuclei are round or oval, frequently folded upon themselves or even highly convoluted with the preservation of their round or oval contour. The nuclei are grayish violet in triacid preparations. Nuclear figures (diasters) are present. Among these cells there are some which show immature and scanty neutrophilic granulation (Giemsa and Jenner stains).

The myelocytes are also extremely variable in morphology, mature forms being scarce. The mononuclear eosinophiles vary in size and degree of differentiation. Some of the granules are rich in basophilic substance. The red blood corpuscles show marked variation in size, shape, and hemoglobin content. There is slight polychromatophilia. Normoblasts and megaloblasts are present. Lymphocytes are present, though their recognition is difficult on account of the large number of small undifferentiated myeloid cells.

Conclusion. The blood is characterized by a preponderance of undifferentiated cells of the myeloid group. A complete series of transitions can be traced from non-granular mononuclear cells with basophilic protoplasm to fully differentiated myelocytes.

Diagnosis. Myeloid leukemia of myeloblastic form with extreme anemia.

CASE II.—*Atypical leukemia with anemia* (?) *or pernicious anemia with leukocytosis* (?) *so-called "leukanemia."* A. S., aged forty-two years, seamstress, German, was taken ill with toothache, swelling, and suppuration of the left cheek, from which she apparently recovered. She came to the hospital complaining of fatigue, buzzing in the ears, headache, and hemorrhage from the gums and into the skin. Physical examination showed extreme pallor of the skin and mucous membranes, hemorrhages in the skin, retina, gums, mouth, and tonsils, enlarged lymph nodes, and an enlarged spleen. There was progressive enfeeblement, a temperature running up to 103.5°, and nosebleed, terminating in death three days after admission to the hospital.

The blood showed 1,790,000 red cells and 45 per cent. hemoglobin, a color-index of 1.2. The white cells numbered 28,000. The differential count was as follows:

Mononuclear non-granular cells	67.4 per cent.
Mononuclears with imperfect scattered neutrophilic granules	11.4 "
Neutrophile myelocytes	6.3 "
Polynuclear neutrophiles	3.6 "
Lymphocytes	11.0 "
Mononuclear eosinophiles	0.3 "

One normoblast was seen for every 500 white cells.

Autopsy reveals enlarged lymph nodes, an enlarged spleen, and complete absence of bone-marrow hyperplasia. In the spleen and lymph nodes the follicles are well preserved and consist almost exclusively of small lymphocytes. The pulp of the spleen and the interfollicular tissue of the lymph nodes show extensive myeloidosis of the myeloblastic type. There is slight hemosiderosis of the spleen and the lymph nodes contain typical megakaryocytes. In the liver there is slight periportal myeloidosis and no hemosiderosis. The appendix is obliterated and shows extreme myeloidosis.

The question of primary anemia or primary leukemia in this case has been discussed before.[6] In spite of the severe anemia, with the high color index and the mild hemosiderosis of the organs, the predominantly leukoblastic type of hematogenesis is sufficient, in our opinion, to warrant the classification of this case as atypical leukoblastic leukemia.

CASE III.—*Osteosclerosis with extramedullary myeloidosis.* J. K., male, aged forty years, was admitted to the second medical division of Bellevue Hospital, having been taken sick on February 19, 1914, with sharp pain in the lumbar region. He quit work in April and from that time on spent most of his time in bed. He came to the hospital complaining of marked pain in the sternal region and dull, aching pain in the right leg. There were no gastric symptoms and no history of cancer. On examination the patient showed extreme pallor, some emaciation, and numerous subcutaneous nodules distributed over the abdomen and chest. There was no jaundice. Enlarged lymph nodes were found in the axillæ and groins. He lost eleven pounds in three months. A roentgenogram revealed the presence of osteoperiosteitis of the pelvis and the shaft of the right fibula. The patient became progressively weaker, and death took place six months after the onset.

The blood examination showed 3,000,000 red cells, 50 per cent. hemoglobin, and 9100 white cells. The differential count was as follows:

Polynuclear neutrophiles	41.0 per cent.
Myelocytes	11.0 "
Myeloblasts	6.0 "
Lymphocytes	23.0 "
Large mononuclears and transitionals	13.0 "
Eosinophiles	2.0 "
Mast cells	0.3 "

Six normoblasts were seen while counting 252 white cells.

The autopsy revealed scirrhous carcinoma of the stomach, with metastases in the pleura, pericardium, peritoneum, omentum, endocardium, myocardium, striated muscles, subcutaneous tissue, and bones. There was osteosclerosis of the osseous system, with obliteration of the marrow in the vertebræ. There was myeloidosis of the spleen and liver.

This case was variously interpreted by different clinicians as acute leukemia with leukemic nodules in the skin, as subcutaneous or metastatic endothelioma, and finally as von Recklinghausen's disease. All that the blood picture really permitted was a diagnosis of either irritative hyperplasia of the bone marrow or vicarious

[6] Meyer, Erich und Heineke, Albert: Ueber Blutbildung bei schweren Anämien und Leukämien, Deutsch. Arch. f. klin. Med., 1907, lxxxviii, 435. Butterfield, E. E.: Ueber die ungranulierten Vorstufen der Myelocyten und ihre Bildung in Milz, Leber und Lymphdrüsen, Deutsch. Arch. f. klin. Med., 1908, xcii, 336.

leukoblastosis and erythroblastosis of the extramedullary blood-forming structures.

CASE IV.—*Purpura hemorrhagica, with severe anemia of a pernicious type.* F. B., male, Spanish, aged twenty-five years, was admitted to the New York Hospital, history No. 202742, on November 3, 1915, complaining of fever, cough, and bleeding from the gums. His family history was negative, there being no knowledge of hemophilia or other familial disease. He has three healthy children, and his wife has had no miscarriages.

He does not recall the diseases of childhood, and denies all venereal infection. He always has been more or less subject to colds, cough, sore throat, and nosebleed, but has not been subject to prolonged bleeding from trauma or to bleeding from the gums. He has been losing weight for several weeks. His present illness began three weeks before admission. His chronic cough became acutely worse, and was accompanied by transitory pains all over his body and by rather severe substernal pain and chilly sensations. After a few days his condition improved so that he suffered only from a chronic cough, which was worse at night, and malaise and weakness. He raised but little sputum and had no hemoptysis. He has not been able to work since the onset of his illness. Twelve days before his admission he again became acutely ill, with fever and cough, but no chills, vomiting, or constipation. His condition continued about the same until the day before his admission to the hospital, when he began to have considerable bleeding from his gums. There was no other bleeding noted. He had some diarrhea a few days before admission, but does not know how long he has been pale or has had the rash.

Examination reveals a rather undersized, fairly well-developed and nourished man lying quietly in bed. He appears acutely ill, but is not dyspneic. The skin is warm, dry, very pale, and white. Small purpuric spots, 1 to 3 mm. in diameter, are very numerous over the feet and legs, less so on the thighs, trunk, and upper extremities. There is no cyanosis or jaundice. No hemorrhages can be seen in the mouth. The sclerae are white and the conjunctivæ pale. The eye-grounds are normal. The mouth and teeth are in poor condition. There is a moderate amount of pyorrhea and the gums are bleeding at the edges, but are not red or swollen. The tongue is protruded in the middle line, and is slightly tremulous and coated. The tonsils and pharynx are normal. Over the apex of the right lung posteriorly the fremitus is increased, and at the spine of the scapula there is tubular breathing and the voice and whisper are increased. No rales can be heard. The heart is not enlarged and no murmurs can be heard. The pulse is of good volume and normal tension, regular in force and rhythm; the vessel wall is not palpable. The abdomen is negative. The liver and spleen are not palpable. There is no general enlargement of the lymph nodes.

Blood cultures and the Wassermann reaction were negative. The sputum was negative for tubercle bacilli. During the first week the temperature varied between 100° and 101°. For the first eight or nine days in the hospital the patient continued to bleed from the nose and throat, and there was considerable blood in the urine. The application of a tourniquet caused the appearance of a fresh number of purpuric spots. From November 8 to 15 there was at first constant diarrhea, with considerable bright red blood, and the urine contained blood. Later the blood in the stool became less and it disappeared entirely from the urine. The patient received 20 c.c. of horse serum on November 6 and 8, and he was transfused with citrated human blood on November 8, 9, 12, and 16, receiving a total of 348 c.c.

The blood examinations were as follows:

Nov.	R. b. c. per c.mm.	Hb. per cent.	Color index.	W. b. c. per c.mm.	Nucleated reds per c.mm.
5	3,810,000	80	1.1	9,600	0
9	1,900,000	40	1.1	15,000	0
11	820,000	25	1.6	28,000	5
13	880,000	21	1.2	26,000	41
15	810,000	18	1.1	30,000	20
17	1,010,000	25	1.3	26,000	9

Among the erythroblasts there are undifferentiated forms, with characteristic nucleus and intensely basophilic, hemoglobin-free protoplasm. Megaloblasts are present. This was a remarkable blood picture, bearing a close resemblance to that seen in pernicious anemia with a blood crisis. The patient gradually grew weaker and died five weeks after the onset.

Autopsy by Dr. William Elser. There are numerous petechiæ in the skin of the feet, legs, and forearms and a moderate number over the trunk, thighs, and upper arm. Pannienlus is moderate and the superficial lymph nodes normal. There is blood about the nostrils and mouth. Pyorrhea is present. There are hemorrhages in the visceral pleura and pericardium. The heart is normal. The lungs are edematous, and there is a small hemorrhagic area in the upper portion of the lower lobe of the left lung. The spleen is small, weighing three ounces, and is normal in consistence. The Malpighian bodies are small and indistinct. The kidneys are normal in structure and size. The pelvis of the right kidney is completely filled with clotted blood, and there are hemorrhages in the mucosa of the bladder. The liver is normal in size, weighing three pounds three ounces. Its surface is smooth and brownish red, and consistence normal. The mesenteric and retroperitoneal lymph nodes are bluish black and dark red in color. The esophagus is normal. There are petechiæ in the stomach, small intestine, and appendix. The lymph follicles and patches are atrophic. The mucosa of the large intestine from the ileocecal valve to the anus

is swollen, dark bluish red, almost black in appearance. The folds and solitary follicles are necrotic. The intestines contain a dark brownish-red, foul-smelling fluid. The vessels running to and from the large intestine appear to be normal. The bone marrow of the upper third of the femur is light red in color, and almost diffluent in consistence. Here and there are small islands of fat. The marrow of the middle segment is of the usual fatty type. Cultures from the spleen are negative even by Rosenow's method. Cultures from the intestinal contents show no organism of the dysentery group. There was the characteristic histological picture of erythroblastic myeloidosis in the blood-forming organs.

The diagnosis in this case lies between *purpura hemorrhagica*, with the marked regeneration common to severe anemias of the pernicious type and *pernicious anemia* proper, with a crisis and complicating subcutaneous and submucous petechiæ. The dominant clinical symptoms as well as the serological findings (note) point to *purpura hemorrhagica vera*.

In the foregoing cases there were three instances of predominantly leukoblastic myeloidosis and one instance of predominantly erythroblastic myeloidosis, and in all cases there was an abundance of transition pictures in the blending between the cells of the predominant group. In these cases most of the cells have prototypes in fetal hematogenesis; cells which departed from the usual manifold transitions in the same groups in intra-uterine hematogenesis and which could possibly be interpreted as degeneration or involution forms were extremely rare. In some cases, however, the development of the white cells seems to take an aberrant course, and the blood picture is dominated by cells which have no prototype in embryonal blood formation; or, more strictly speaking, if such embryonal prototypes occur they are at least extremely scarce in the blood and blood-forming organs of the human embryo. It is very difficult to classify these cells, in which there appears to be a loss of coördination between the development of the nucleus and the differentiation of the protoplasm. A leukemic picture with a predominance of such cells has been described in chloroma,[1] and one of these unusual cases is briefly reviewed here. Two additional cases are also described, one showing a predominance of the same type of cell in a leukemic blood picture and the other a predominance of these cells in a leukopenic blood picture.

CASE V.—*Chloroma.* A. R., male, joiner, aged twenty-four years, caught cold four weeks before admission to the hospital and suffered from cough, toothache, and swelling of the glands of the neck. One week before admission he began to suffer from weakness, shortness of breath, and palpitation. He had much pain in the neck and intense salivation, and was able to swallow only liquid

[1] Butterfield, E. E.: Beitrag zur Morphologie der Chloromzellen, Fol. hemalol., 1909, viii, 179.

food. Four days before admission he became so weak that he was confined to bed. During the last two days numerous pin-point hemorrhages have appeared in the skin over the whole surface of the body. On examination the muscles were found to be poorly developed and the subcutaneous fatty tissue scant. There was general enlargement of the lymph nodes, which is extreme in both cervical regions. There were numerous petechiæ in the skin but none in the retinæ. The gums were thickened, loose, and bleeding. The heart was negative. The spleen was enlarged and firm. The edge of the liver was palpable, its dulness extending two finger-breadths below the costal margin. The temperature varied from 101° to 103°. The urine contained albumin and much iron.

The blood examination showed 3,400,000 red cells and 60 per cent. hemoglobin. The white cells were 60,000 and later rose to 200,000. The differential count was as follows:

Mononuclear cells, non-granular with convoluted nucleus	80.4 per cent.
Mononuclear cells with imperfect and scattered neutrophilo granules	7.0 "
Myelocytes	1.6 "
Lymphocytes	4.0 "
Mononuclear eosinophiles	0.4 "
Definite plasma cells	0.6 "

Two normoblasts were seen while counting 1000 white cells.

All transitions were seen from the dominant cell to the neutrophile myelocyte, while some of these cells showed scattered neutrophile and eosinophile granulations. The dominant cell was a peculiar one. The nuclear structure could be made out only with difficulty. When well stained the nucleus was seen to be folded and convoluted, often in a most intricate fashion. The protoplasm exhibited all grades of basophilia, and contained at times granules which were demonstrated with difficulty, but which reacted similarly to those seen in myeloblasts. The cells apparently belonged to the myeloid series.

The autopsy showed an enlarged liver and spleen and enlarged lymph nodes, which were definitely and distinctly green. There was no hyperplasia of the bone marrow of the femur or ribs. In the spleen the Malpighian bodies could not be recognized. There was periportal myeloidosis in the liver and interfollicular myeloidosis in the spleen and lymph nodes.

This case represents the last word in atypical leukemia, in that the dominant cell has no prototype in normal fetal or postfetal hematogenesis. While this same cell showed definite myelocytic transitions there was a total absence of hyperactivity on the part of the bone marrow, and the chief site of non-lymphocytic leukoblastic proliferation was in the *interfollicular* tissue of the spleen and lymph nodes.

CASE VI.—*General enlargement of the lymph nodes; leukemia; lymphatic tuberculosis.* I. B., male, Hebrew, aged forty years, was admitted to the New York Hospital, October 21, 1913. History No. 191055. He had always been well before the present illness. Twenty years before he had gonorrhea and a questionable lesion on the glans. Two or three months before admission he noticed hard, movable, non-painful swellings in his groins. One month before admission his wife and friends noticed that his abdomen was growing larger. He had no pain until one week before admission, when it began to be present, always under the right costal margin, coming on immediately after eating and lasting about five minutes. It was never severe. There was no nausea or vomiting. On examination the patient was seen to be well developed and nourished. He had slight pyorrhea. The tonsils were not enlarged. The lungs were negative. The heart was not enlarged, though there was a systolic murmur heard loudest at the apex and not transmitted. The pulse was regular and of good force. The lower edge of the liver extended 11 cm. below the xiphoid in the middle line. In the abdomen, above the umbilicus and to the left was a hard mass, about 6 x 9 cm. in size, the outer edge of which could be felt distinctly in the mammary line. The right edge could be felt through the rectus to the left of the umbilicus. There were no other masses. The spleen could not be felt. There was some shifting dulness in the flanks. There were collections of about six olive-shaped glands, about 4 cm. long, readily felt in each groin, and there were similar masses in both supraclavicular regions and axillæ. The urine contained no albumin or sugar. The Wassermann reaction was negative. The gastric contents contained no free hydrochloric acid, but did contain blood. There was a slight loss of weight during the patient's stay in the hospital.

Examination of the blood revealed the following:

Date.	R. b. c.	Hb., per cent.	W. b. c.	Non-gran. mono., per cent.
Oct. 21	6,400,000	87	68,000	75
24	5,100,000	90	101,000	89
Nov. 1	5,300,000	80	87,000	92

Most of the non-granular mononuclears showed a folded or convoluted nucleus and undifferentiated protoplasm. It is impossible to make out any transitions from these cells to any known elements in the human blood or blood-forming organs.

A lymph gland was excised, part of it examined histologically, and the remainder injected into a guinea-pig. The pig died in eighteen days, having developed extensive tuberculosis. The spleen and liver of this animal were injected in part into two other guinea-pigs, each of which developed tuberculosis, and died in the course of thirty days. The histological appearance of the excised node was

peculiar. There were round collections which resembled follicles on superficial examination. On closer examination they were seen to consist chiefly of cells with folded and convoluted nuclei similar to those seen in the peripheral blood. The interfollicular tissue consisted largely of the same type of cell; in fact, practically all the details of the normal lymphatic gland were absent. The appearance was not unlike a granuloma. The patient soon left the New York Hospital and went to the General Memorial Hospital, where, under benzol treatment, the leukocyte count was reduced from 50,000 to 10,000. From December, 1913, to July, 1914, the count varied between 10,000 and 20,000. The lymph nodes were reduced to one-third of their previous size. In July, 1914, in spite of benzol and roentgen-ray treatment, the count rose rapidly until it reached 60,000 on August 17, and the patient died a little over a year after the onset of symptoms. No autopsy was obtainable.

This case was obscure and indeterminate. The blood picture points to an atypical leukemia, while the histological and experimental data were indicative of a lymphatic granuloma, possibly tuberculosis. The long-sought relation between a leukemic blood picture and an infectious substrate may rest, unrevealed, in this case.

CASE VII.—*Obscure acute infection with atypical blood picture.* J. B., male, aged thirty-three years, was admitted to the New York Hospital August 9, 1915. His appendix had been removed six and a half years before. The onset of his present illness was marked fever, anorexia, and pain over the region of the liver. He felt weak and nauseated, and vomited at times. He had passed blood by rectum.

The patient was a large, well-nourished man, somewhat pale. The teeth were in fair condition and free from pyorrhea. The tonsils were enlarged and reddened. The lymph nodes were moderately enlarged, the epitrochlears were not palpable. The lungs were negative. The heart was enlarged and the pulse soft and dicrotic. The abdomen was negative except for the scar of his appendectomy operation. The liver and spleen were not palpable. There were scars over the tibiæ but no edema or tenderness.

The blood examinations showed the following:

Date.	R. b. c.	Hb., per cent.	W. b. c.	Non-gran. monos.	Polys., per cent.
Aug. 10	3,800,000	73	6800	98	2
20	....	..	7800		
Sept. 5	2,240,000	50	3800		

The non-granular mononuclear cells were in great preponderance and were essentially the same in type as those seen in Case VI. The polynuclear neutrophiles were almost absent.

The urine contained no albumin on admission, but on August 26 albuminuria appeared and remained until death. The temperature

ranged between 101° and 105°, usually above 104°. The lymph nodes enlarged so that by August 18 practically all the superficial nodes were distinctly swollen and the spleen and liver were palpable. There was a phlebitis in the left leg. The following day a pericarditis developed. On August 23 the phlebitis was diminishing and the gums were swollen and red, though not bleeding. By August 29 the gums became very sore and began to bleed, and the tonsils were much swollen. The following day there were signs of fluid in the left chest and 250 c.c. were removed. The fluid was pink in color and a culture revealed the presence of the Bacillus pyocyaneus. By September 1 the tonsils had so increased in size that they met in the middle line. On September 3 the chest was again aspirated and 400 c.c. of fluid removed. The Bacillus pyocyaneus was recovered from this specimen also. Roentgen-ray examination showed an enlarged heart and a mass of enlarged bronchial lymph nodes above it. The Wassermann reaction was negative and two blood cultures remained sterile.

Autopsy. The autopsy revealed a mass of enlarged bronchial lymph nodes, one gland measuring 3.5 cm. in length. The liver weighed 2400 gm. The spleen was enlarged. There was some perisplenitis and the follicles were not visible. The bone marrow was grayish yellow and somewhat gelatinous.

This case was by far the most obscure of all the atypical cases discussed. All of the familiar earmarks of an infection are present and the ordinary and the most refined methods of bacteriological search and analysis failed to reveal any known pathogenic organism. The cytological analysis showed a predominance of cells identical with the atypical cells of the two preceding cases, but the predominance in this case is only relative and the absolute number of all white cells was either normal or diminished.

These cases serve to illustrate the difficulty in diagnosis even with the aid of the most improved methods and with the histological evidence before us. They also illustrate the inadequacy of present therapeutic measures. Benzol, roentgen ray, faradization, transfusion, and splenectomy may produce fluctuations in the blood picture, and these fluctuations may be interpreted as improvements if one so desires; but the essential diseases of the blood-forming organs still run their usual course. This should not be a cause for pessimism and discouragement, but should stimulate to more active and consistent work until some fortunate group of workers find the clue which will throw some light upon the etiology of these conditions.

NOTE.—We are indebted to Dr. Witt for the results of the serological investigation. He was able to show that the greatly delayed coagulation time in this patient was associated with a diminution in the platelets, which numbered but 1000 per c.mm., and an increase in the antithrombin. The other elements in the coagulation reaction were apparently normal.